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Profile of Orbital Involvement in Covid Associated Mucormycosis: A Tertiary Health Care Centre Experience in North India

Ashutosh Maharana[1], Nibha Mishra[1], Ritu Singh[1], Reena Bharti[1], Devanand Bharti[1], Apjit kaur[1]
[1]Department of Ophthalmology, King George's Medical University, Lucknow, India

***Corresponding Author:**
Apjit Kaur
MS, FAICO, PGDHHM, Professor and Head, Department of Ophthalmology, King George's Medical University, Lucknow, India. 226003

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Abstract

Purpose: To study the profile of orbital involvement and the risk factor analysis of Rhino-orbital-cerebral Mucormycosis (ROCM) during the second wave of COVID-19 in a tertiary health care centre in north India.

Design:Tertiary health care centre based retrospective descriptive study.

Methods:214 consecutive cases of Mucormycosis admitted during the period from May 2021 to July 2021 with concurrent or recent history (less than six weeks) of COVID-19 were included. Demographic, clinical and management profile of the patients were evaluated.

Results: Mean age of the patients in the present study was 50 $\pm$ 11 years, majority being male (64%) and from rural background (53.7%). Type II diabetes mellitus and corticosteroid use were the most common risk factor for ROCM. The clinical spectrum of orbital involvement included orbital pain, diminution of vision, lid and periorbital edema, drooping of eyelids, conjunctival chemosis, proptosis and limitation of extraocular movements. Among the patients with vision loss two routes of orbital involvement were noted. One with extensive orbital involvement leading to optic neuritis, orbital apex syndrome or superior orbital fissure syndrome, suggestive of direct spread from paranasal sinuses (PNS). Other group had minimal orbital involvement with retinal vascular occlusion suggestive of indirect spread. Besides systemic antifungal and PNS debridement, orbital management was done by retrobulbar trans-cutaneous amphotericin B injection (190 patients) and exenteration (18 patients).

Conclusions: Orbital involvement in ROCM has a wide clinical profile, and route of spread. Proper assessment of risk factors and clinical features with early diagnosis and aggressive management can lead to better survival.

Keywords: Rhino orbital cerebral Mucormycosis, COVID-19, direct invasion, indirect spread, North India

Introduction

In the era of COVID-19 pandemic, Mucormycosis has emerged as an important opportunistic fungal infection and has become a serious public health concern in India[1-4]. States of immunosuppression such as diabetes mellitus, immunodeficiency states, malignancies organ transplantation and, deferoxamine therapy predispose the individuals for Mucormycosis[5,6].

Nasal structures and paranasal sinuses are initially involved, followed by orbital and central nervous system involvement subsequently[7-10]. Orbital involvement leads to proptosis, chemosis, ophthalmoplegia and loss of vision[10-13]. The presentation is typically a rapidly progressive infection, and the disease is associated with a high morbidity and mortality rate.

The aim of the present study wasto analyse the profile of orbital involvement, risk factors and management of Rhino-orbital-cerebral Mucormycosis

(ROCM), during the second wave of COVID-19 in a tertiary health care centre in north India.

Methods:

The study authors, confirm adherence to the tenets of the Declaration of Helsinki. This study was conducted after the approval by the Institutional Ethics Committee.It is a tertiary health care centre based retrospective data analysis study. 214 consecutive suspected cases of Mucormycosis with concurrent or recent history (less than six weeks) of COVID-19 infection, over a three months period from May 2021 to July 2021 were included. A multidisciplinary team was appointed for the management of Mucormycosis patients at our tertiary health care centres. Diagnosis of COVID-19 was made on RTPCR (reverse transcriptase polymerase chain reaction) test. Diagnosis of ROCM was made on the basis of magnetic resonance imaging (MRI) based radiological findings, KOH (potassium hydroxide) mount of nasal swab samples or histopathological examination for fungal elements of samples from nasal debridement.

All the patients were evaluated for the demographic parameters which included age, sex and locality. A detailed clinical history was taken to elicit various systemic involvement and associated of risk factors. Risk factors analysed were diabetes mellitus, previous steroid usage, oxygen supplementation, prior ventilator usage, hypertension and any other cardiac or respiratory comorbidities.

A thorough ophthalmic bedside clinical examination was done. The orbital symptoms and signs that wear analysed were i.e. diminution of vision (DOV), orbital pain, chemosis, proptosis, drooping of eyelids, eyelids edema, ocular movement limitations. Posterior segment findings were recorded via smartphone-based technology which is performed bedside. We categorise DOV as severe and non-severe, severe DOV being finger counting close to face, perception to light (PL) present and PL absent (PL denied).

Relevant blood investigation andMRI head, orbit and paranasal sinuses with contrast were performed. Radiological staging of orbital disease was done as per the published institutional protocol[4].

All the patients received systemic treatment as per the protocol[4]. Medical management was based on the general medical condition, comorbidities, hepatorenal status and stage of the disease. Induction therapy started with liposomal Amphotericin-B (LAmB) 5mg/kg/day (10mg/kg/day if brain is involved). Where LAmB was contraindicated intravenous or oral Isavuconazole 200mg 8 hourly on days one and two followed by 200 mg once a day from day three onwards given. Alternately intravenous or oral Posaconazole 300mg 12 hourly on day one followed by 300 mg once a day from day two onwards can be given.

Ophthalmological intervention included Transcutaneous Amphotericin B (TRAMB), orbital debridement and exenteration as per the institutional protocol[4]. Lateral temporary tarsorrhaphy was performed in patients for severe proptosis with risk for exposure keratopathy). Patients having minimal orbital disease were planned for TRAMB. Minimal orbital disease is characterised by the following:

1. Vision unaffected/reduced
2. Chemosis present or absent
3. Mild proptosis (<3mm)
4. Mild or no resistance to retropulsion
5. Extraocular movements preserved/ terminally restricted
6. Fundus normal/CRAO
7. Orbital imaging suggested of limited disease (medial quadrant involvement)
8. patient unfit for surgery

Moderate to severe orbital disease is characterised by the following:

1. Vision reduced/lost
2. Chemosis present
3. Moderate to severe proptosis
4. Significantly positive retropulsion
5. Restricted ocular movements or frozen globe
6. Fundus disc edema/CRAO/no visibility due to media haze
7. Orbital imaging extensive orbital involvement

Patients having medial orbital involvement (medial orbital wall osteomyelitis) on orbital imaging were planned for orbital debridement along with sinus debridement. Those patients having moderate to severe orbital disease were planned for orbital exenteration.

Results

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The number of patients included in our study were n=214. Age distribution in our study ranged from 22 - 82 years with mean age 50 ± 11 years. Out of 214 patients 139 (64%) were males and 76 (36%) were females. 116 (53.7%) of the total patients belonged to the rural background.

On risk factor analysis we noted that 173 (80.8%) had history of Type II diabetes mellitus (controlled on oral hypoglycaemic agents and insulin), 99 (47.1%) patients had a history of steroid intake, 96 (44.8%) patients had a concurrent history of COVID-19 infection, 55 (25.7%) patients had hypertension, four (1.8%) patients had coronary artery disease,two (0.9%) patients had asthma and two (0.9%) patients had history of ventilator usage (figure 1).

The visual symptoms range from being asymptomatic to no perception to light. 79 (37%, n=214) patients had severe DOV ranging from finger counting close to face to denied perception to light, at the time of presentation. 19 (8.9%, n=214) were altered to the extent that vision assessment couldn't be done. Orbital swelling (65.9%, n=214) is the most prevalent symptom encountered in our patients. Other symptoms and their occurrence are depicted in the graph (figure 2). Among the orbital signs, lid edema (65.9%) is most frequently encountered (figure 3). 48 (22.4%, n=214) patients had central retinal artery occlusion (CRAO) on posterior segment evaluation at the time of presentation. Out of all the cases of severe DOV (n=79), only 39.2% had CRAO.

On radiological evaluation, 42 % of the cases had stage 4 ROCM and 38.8% had stage 3 ROCM. Out of all the cases of severe DOV (n=79) 12.7% had stage 2, 30.4 % had stage 3 and 57% had stage 4 ROCM . 210 (98%) patients had deranged CRP levels above 6 mg/l, 203 (94.9%) patients had serum d-dimer above 0.5 ug/ml, 190 (88.8%) patients had serum IL-6 levels above 5 mg/mL, 178 (82.8%) patients had serum ferritin levels above 230 ug/l and 177 (82.7%) patients had uncontrolled diabetes mellitus.

190 patients (88.7%) were given three consecutive transcutaneous retrobulbar liposomal Amphotericin B (3.5mg/1ml). 99% (n=190) of patients who received TRAMB had favourable outcome in terms of halt or reversal of course of disease. One patient showed local tissue necrosis because of the TRAMB injection. 18 patients underwent orbital exenteration. Six patients died, giving case fatality rate of 2.8%.

Discussion:

We have documented various spectra of orbital involvement along with the demographics and risk factors analysis of the patients of Mucormycosis in the second wave of COVID infection in India. As our institute is a tertiary care referral centre having state of the art medical care facilities in northern India, we deal with various spectra of disease.

Our centre treated 214 patients of Mucormycosis-ROCM within a period of three months that shows the gravity of this condition in the current COVID scenario. Male population from rural backgrounds in late adulthood were the most susceptible ones. Nearly half of the patients had a history of concomitant COVID-19 infection and steroid intake. Both of these conditions led to a state of hyperglycaemia which compounds the situation in a patient with prior history of diabetes mellitus. We had 80.8 % of patients with prior history of type II diabetes mellitus. Other comorbidities that our patients had included history of hypertension, coronary artery disease and asthma. These factors may directly or indirectly affect the immune condition of the patient. Various pathophysiological interplay could be possible with the novel COVID-19 infection which had resulted in the rise of this dreadful fungal infection.

Mucormycosis is a vaso-occlusive disease and results in necrosis and ischemia of the tissues[14,15]. The resultant vascular thrombosis prevents the drugs from systemically reaching the infected tissue. Moreover, the angio-invasion allows the organism to disseminate to other organs.

Initially this disease affects nasal and paranasal structures that includes sinuses and muscles and soft tissues of upper jaw and pterygoid fossa eventually spreading to the adjacent orbits and finally the brain[7-10]. Spread to the orbit occurs most commonly through the direct invasion of medial and inferior wall, and into the brain through the nerves, arteries, superior orbital fissure, optic canal or via the carotid vessels[16]. Besides direct spread, Mucormycosis can also have indirect vascular spread because of its agio-invasive nature compounded by hypercoagulable state. Vascular spread will more likely results in involvement of the posterior segment of eye in the form of retinal vascular occlusion. In present study the clinical spectrum of orbital involvement included orbital pain, lid and periorbital edema, drooping of

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eyelids, conjunctival chemosis, proptosis, limitation of movements ranging from mild limitation to frozen eye, corneal abscess with corneal melting and medial orbital nodular skin swelling. Orbital pain and lid edema were the commonest clinical presentation. Vision involvement of these patients ranged from asymptomatic to denying perception of light. We found in our study that 79 patients had severe vision loss out of which 31 (39.2%, n=79) had CRAO without much features of orbital involvement and 48 had vision loss with marked signs of orbital involvement. Moreover, 12.7% (n=79) of cases with severe DOV had stage 2 ROCM, which further suggest an indirect route of orbital involvement in Mucormycosis. There is a positive corelation between CRAO and increasing severity of the disease. Our novel study thus highlights that clinical spectrum of ophthalmic findings depends on the route of spread that are direct (figure 3) and vascular (figure 4).

Among the laboratory parameters, inflammatory markers like CRP, IL-6 and D-dimer were raised in a significant number of patients. We have also seen that most of our patients presented with stage 4 ROCM. Angio-invasive nature of the disease in a susceptible individual results in a poor prognosis projected via the worsening symptoms and signs along with greater severity of the radiological staging of ROCM and deranged laboratory parameters.

The primary aim in surgical intervention is to achieve debridement of all necrotic tissues. Drainage of paranasal sinuses and orbital exenteration can be lifesaving in the presence of an active fungal infection[17].Successful treatment of Mucormycosis is dependent on four key principles: early diagnosis, treatment of underlying predisposing factors, surgical debridement of necrotic tissue, and administration of antifungal therapy[18]. 18 patients underwent orbital exenteration in our study. Because of the debilitated medical condition of ROCM, it doesn't allow for the preanesthetic clearance (PAC) in many cases. 88.7 % of our patients were managed with TRAMB. Cost effectiveness of this therapeutic management options along with the ease with which it can be administered even in debilitated patient in whom exenteration couldn't have been done otherwise, tempted us to proceed with this experimental option. It allows us to deliver the antifungal drugs at places where intravenous drug penetration couldn't otherwise be possible because of the ischemia and necrosis. TRAMB had some promising outcome in our experience, however its long-term safety and efficacy are needed to be studied. 18 patient underwent orbital exenteration, out of which one died on the second postop day because of the low general condition of the patient. Long term of the effect of orbital exenteration also further needed to be studied.

Patients seem to be more concerned with the involvement of the eyes as it is not only easily visible but also gives cosmetic deformity. We all are familiar with the overburden situation going on in this COVID era. With the rise in this dreadful and disfiguring condition the situation has worsens. So this burden is to be shared by ophthalmologists and primary health care physicians both. Having a high index of suspicion, targeting the susceptible population having the implicated risk factors, we can detect this dreadful disease early in its course, and can spare the person from a lifelong comorbidity and even death.

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Figures

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Figure 1. Bar graph analysis showing numbers of patients with risk factors for Mucormycosis. Most common were type II diabetes mellitus, corticosteroid use, and COVID-19 infection.

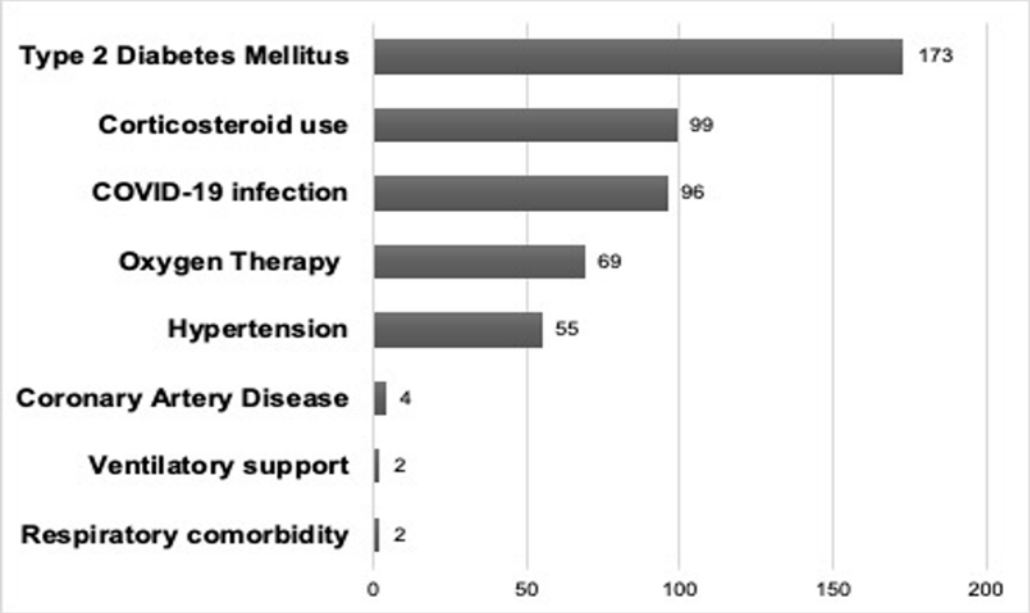

Figure 2. Bar graph showing number of patients with the orbital symptoms of ROCM. Most common symptom was lid swelling

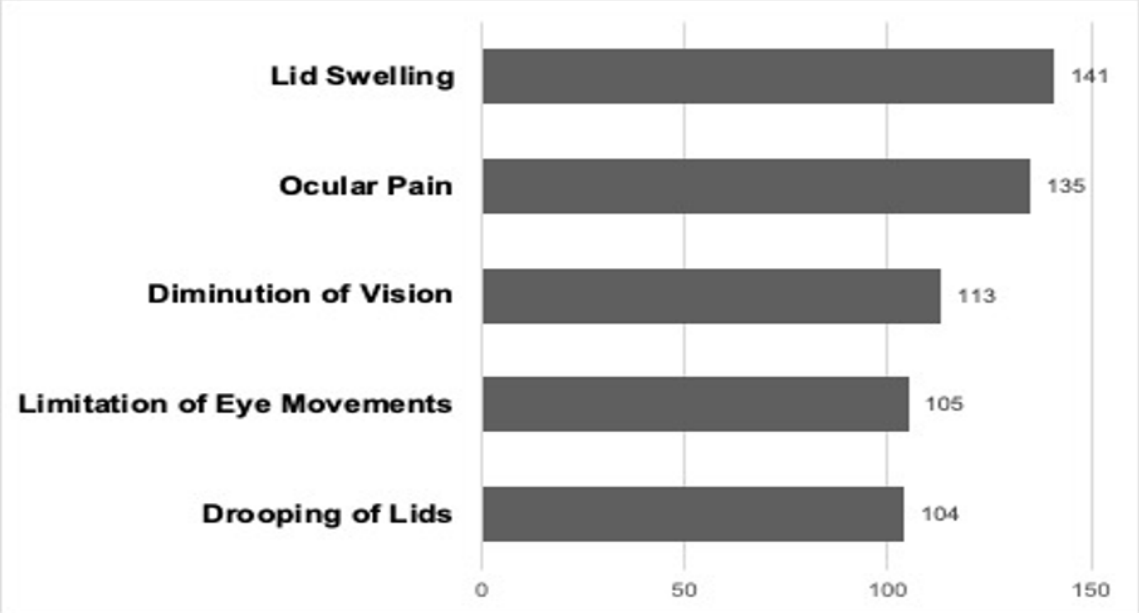

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Figure 3. Bar graph depicting the number of patients with orbital signs of ROCM. Most common orbital sign encountered was lid edema

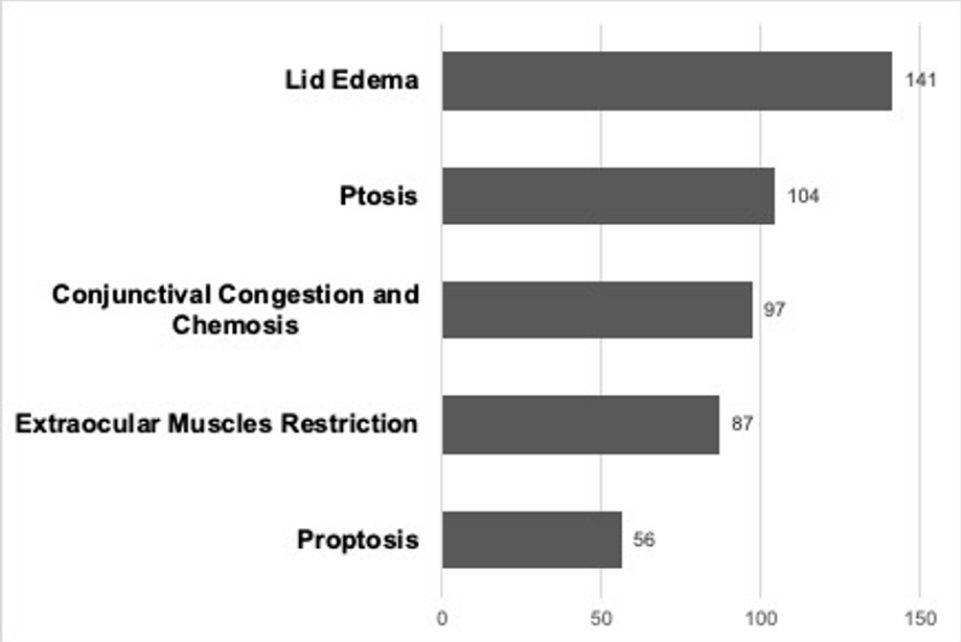

Figure 4: a) Direct spread ofMucormycosis into the orbit from paranasal sinuses. b) On lid retraction severe chemosis and congestion seen, no posterior segment view. c) Axial T2 weighted MRI showing features of extensive involvement of right orbit, superior orbital fissure and cavernous sinus.

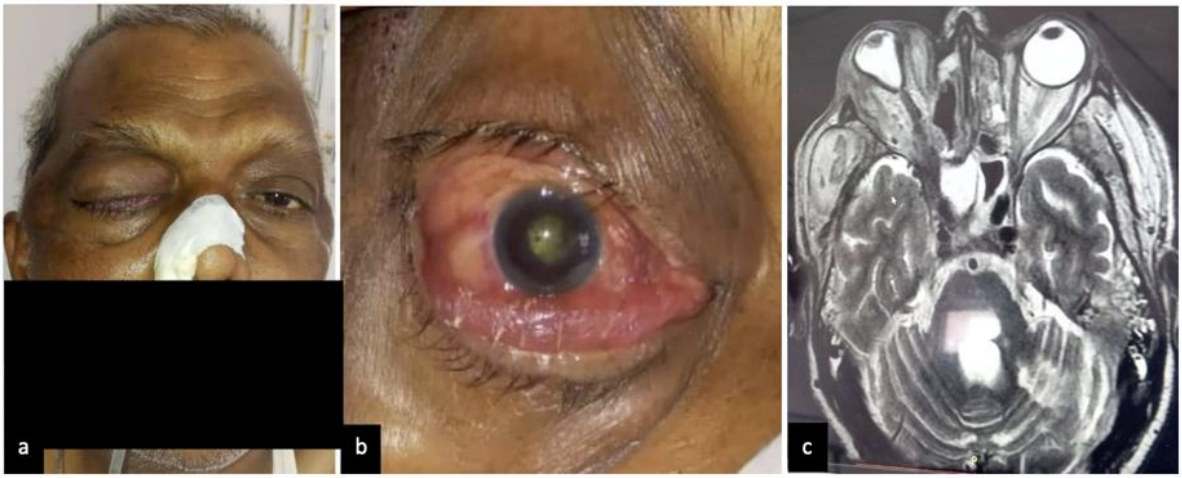

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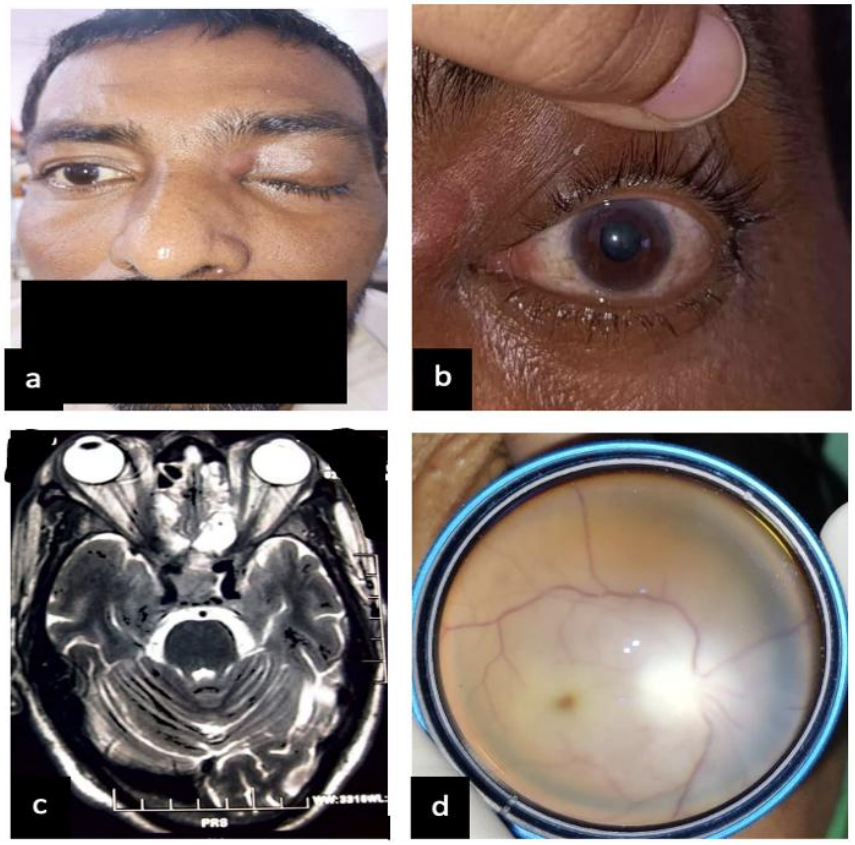
Figure 5. a) Indirect spread of Mucormycosis into the orbit with vascular occlusion. b)On lid retraction apparently quiet eye seen but with no perception to light c) Axial T2 weighted image showing minimal involvement of left orbit. d) central retinal artery occlusion in posterior segment



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